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INTRALESIONAL TRIAMCINOLONE AND ADRENAL SUPPRESSION IN ACNE VULGARIS*

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ABSTRACT

Adrenal suppression was investigated in nine patients with acne vulgaris whose inflammatory cysts were injected with triamcinolone acetonide. Using this steroid, total doses of 20 mg or more delivered into numerous sites at one time were required to produce suppression of plasma cortisol by fluorometric analysis. Clinical evidence of systemic absorption was suggested by overall improvement in the acne process including not only sites injected, but also those distant from injection. The apparent clinical improvement in uninjected sites together with laboratory evidence of plasma cortisol suppression persisted for at least five days when a total dose of 50 mg of triamcinolone acetonide was employed.

Although only plasma cortisol levels were observed, a parallel suppressive effect on adrenal androgens such as dehydroepiandrosterone would contribute to any overall improvement in the acne process. The relative importance of adrenal androgen suppression compared to the direct effect of the systemically absorbed exogenous steroid remains unanswered.

While in many cutaneous diseases, including acne vulgaris (1, 2), topical corticosteroids are both effective and often used preparations, it has been shown in a number of investigations that these drugs may be absorbed in sufficient amounts to cause adrenal supression (3–6).

The differences in manner of administration and vehicle; combination with occlusion and variable usage time can lead to uncertainty in assessing the probability of suppression or its duration in a clinical situation. The proposed ideal of a minimal effective dose, not known to affect adrenal function, becomes more difficult to appreciate on an outpatient basis than in a carefully controlled investigational setting. Also, there is still a need to correlate steroid dosage with duration of suppression.

Intralesional corticosteroids are used in some of the more localized cutaneous reactions (7–9) and in some instances are more suitable than topical application. Perhaps one of the most common diseases in which this is true and in which intralesional steroids are widely used is acne vulgaris with inflammatory cysts (10, 11).

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It was decided to study the relationship between the suppressive intralesional dose and the duration of suppression, having observed that a close comparison would prevail between the clinical and investigational setting. The similarity is permitted by the relative homogeneity of the patients with acne, as well as by other factors of timing, method and direct supervision of drug administration. In a study by Gill and Baxter (4) a single patient receiving 45 mg of triamcinolone acetonide intradermally was shown to have adrenal suppression for at least 96 hours, as measured by fluorometric plasma cortisol determination, while McGugan, *et al.* (12) had reported that doses of 75 to 100 mg were required to produce measurable adrenal suppression, using the Porter-Silber method of plasma cortisol determination. Comparison of these and similar studies of adrenal suppression and responsiveness indicate that the methods of determination, as well as administration, are variable in accuracy and may also limit accurate quantification. The present study is subject to the same limitations, as will be noted later in the text.

METHODS

Nine patients were selected, all of whom were young, healthy males, ages 19 to 25. All had severe acne with numerous cysts and conglobate lesions of the trunk and, to a lesser extent, of the face and buttocks. None had received previous corticosteroid treatment. All were hospitalized and main-

tained in as nearly identical a routine as possible with blood samples for plasma cortisol taken between 7 a.m. and 8 a.m. The samples were analyzed on the day obtained following immediate separation of plasma. After one or two baseline samples, 15 to 50 mg of triamcinolone acetonide at a concentration of 5 mg/cc diluted from a standard commercial preparation of 40 mg/cc with 1% aqueous xylocaine was injected into the inflammatory acne cysts of the nine patients. Further blood samples were analyzed daily on the succeeding four to 14 days as required by the evolution of the individual pattern of response. The fluorometric procedure for free 11-hydroxycorticoids described by Mattingly (13) was employed, and is referred to a "plasma cortisol".

All patients were continued on an identical regimen of tetracycline, topical keratolytics and dietary precautions while in the hospital. No acne surgery was employed during the study, nor were any topical steroids or steroid-containing preparations used.

RESULTS

Although only one baseline plasma control level was obtained for most patients, there was little fluctuation in the day to day levels after return to normal (see Table). Unfortunately, the amount of triamcinolone injected does not always remain intralesional as minute amounts can usually be seen returning back through the injection site onto the open skin. Although care in avoidance of back flow and cyst rupture was practiced, the amount stated to be employed was always some small variable amount larger than that actually deposited in the cyst.

Only one patient had cystic involvement extensive enough to actually accommodate an intralesionally injected total volume of 10 cc or 50 mg of triamcinoline acetonide (5 mg/cc). Suppression in this patient as determined by plasma cortisol levels was marked at 24 hours and persisted for 5 days (Figure 1). However, it was believed that the number and size of cysts in this patient would rarely be encountered among acne patients.

Two patients receiving 35 mg total dose (Figure 2) and four patients receiving 20 mg total dose (Figure 3) also had extensive involvement considered uncommon, yet of the type frequently seen in dermatologic practice. These patients showed suppression of 1 to 3 days duration.

Two patients who received 15 mg (Figure 4) did not show suppression at any time during the routine, a finding which denotes a trend, not a decisive separation between dose requirements for suppression.

Finally, overall temporary improvement in the acne process including sites not injected was noted. This was demonstrated in one patient receiving 20 mg distributed over all areas excepting one severely involved side of his face. This somewhat unexpected finding, seen in the seven patients receiving the 20 mg or larger dose, was unfortunately discovered after adequate photographic documentation could be made. In the absence of placebo injection studies, it should be regarded as tentative.

DAILY VALUES OF PLASMA CORTISOL (μg) FOLLOWING VARIOUS DOSES OF TCA°

		DAYS FOLLOWING TREATMENT													
		C*	1	2	3	4	5	6	7	8	9	10	11	12	13
PATIENTS RECEIVING 50mg INTRALESIONAL TCA.	I.B.B.	13.5	3.5	6	5	4	4	9	12	11.5	11.5	14	8	19	18
PATIENTS RECEIVING 35mg INTRALESIONAL TCA	2.S.W.	18.2/13.5	5	1.4	15	13	18	18.2	20	16	22				
	3.T.B.	18/21	9	9	21	25	12			23					
PATIENTS RECEIVING 20mg INTRALESIONAL TCA	4.J.R.	23	6.5	20	13.5										
	5.B.P	22	5.1	19											
	6.F.A.	17	4	10.2	10										
	7.C.K.	12.5	3	16	16	14.5			20						
PATIENTS RECEIVING 15mg INTRALESIONAL TCA	1.J.T.	19	15	16	16										
	2.F.H.	17.8	25	24.2	20.4										

C* CONTROL DAY OR DAYS PRIOR TO INJECTION
° TRIAMCINOLONE ACETONIDE

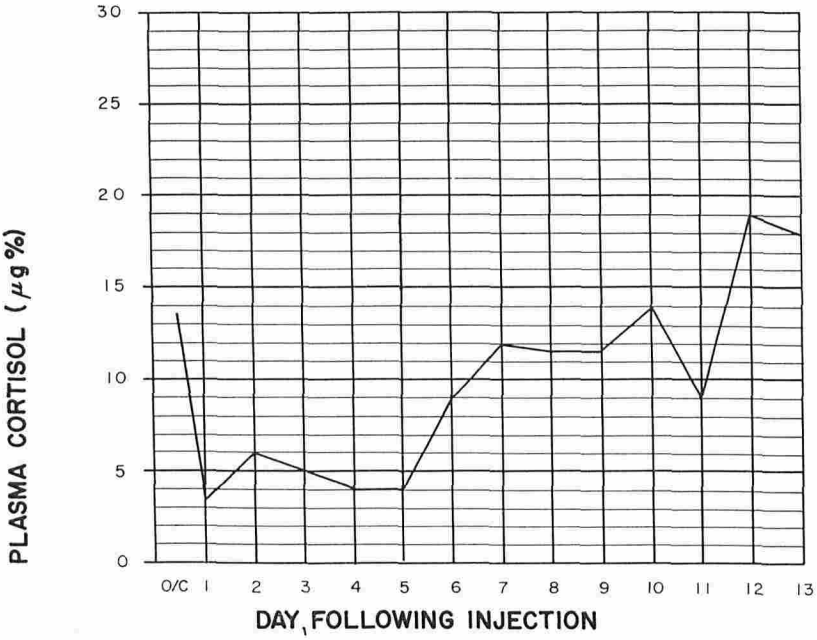

FIG. 1. Pattern of daily plasma cortisol following 50 mg intralesional triamcinolone acetonide.

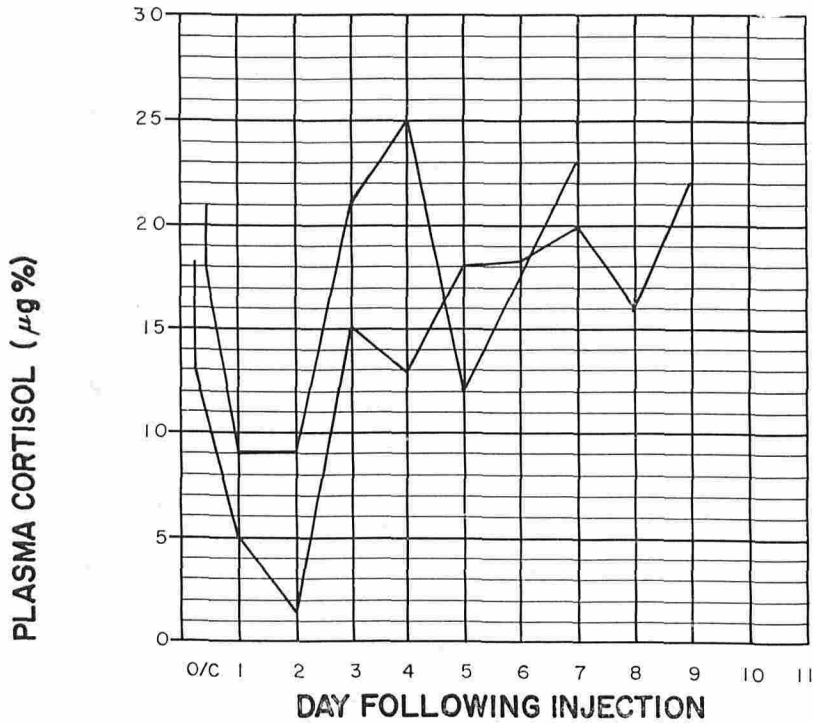

FIG. 2. Pattern of daily plasma cortisol following 35 mg intralesional triamcinolone acetonide.

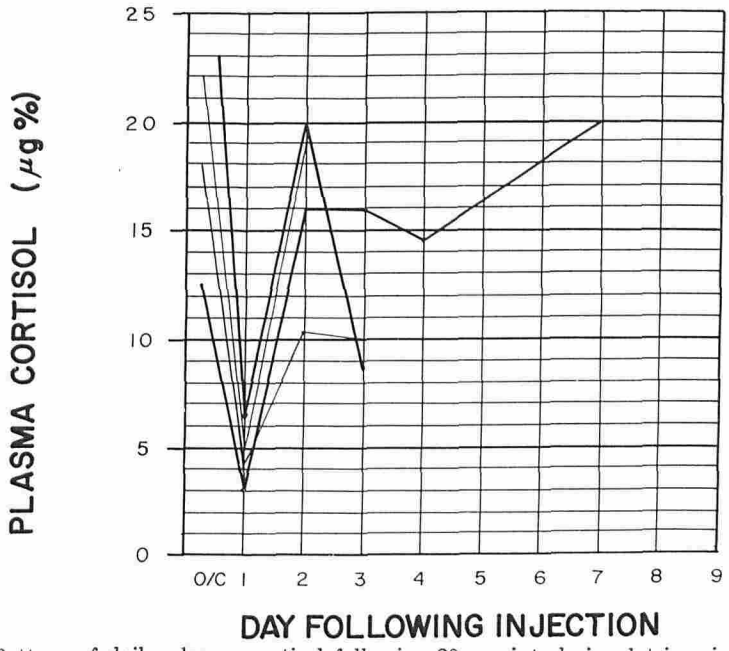

FIG. 3. Pattern of daily plasma cortisol following 20 mg intralesional triamcinolone acetonide.

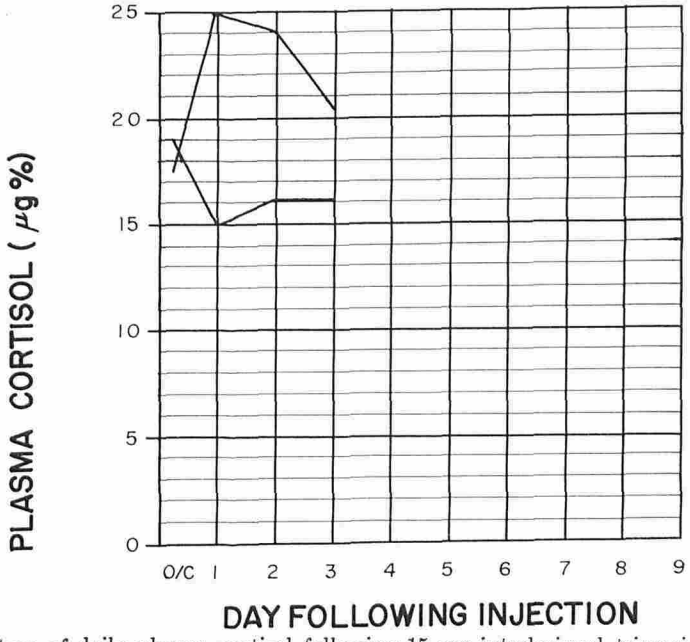

FIG. 4. Pattern of daily plasma cortisol following 15 mg intralesional triamcinolone acetonide.

COMMENT

Intralesional injection of triamcinolone acetonide at sufficient dosage in cystic acne induces adrenal suppression, the duration of which seems dose dependent. The degree of suppression would best be measured by functional reserve during stress. Such measurements were not demonstrated, but would be expected to share a similar

relationship to the dose. The pattern of return of plasma cortisol values to normal in 2 to 6 days after the early suppression at 24 hours fails to support the concept of an expected prolonged absorption due to the insolubility of the steroid and its intralesional site. However, this may be a reflection of the lack of refinement in measuring the degree of suppression and if the total dosages used had been larger, a prolonged absorption phase of significant magnitude might then have been observed to offset the rapid return of plasma cortisol to normal as seen in these cases.

The lack of demonstrable suppression at 2 days in the subjects receiving 20 mg, together with the clinical flaring of acne within a few days after return of plasma cortisol levels to normal, also suggests that the duration of suppression is related to dose without significant delayed effects from any prolonged absorption that may occur at relatively lower doses.

In the patients studied, there was a noticeable improvement occurring during the 1 to 5 day suppression of plasma cortisol in those inflammatory lesions not injected. This general improvement appeared to be greater than that which could be attributed to other ongoing factors in treatment and was moreover, followed by flaring with appearance of new lesions shortly after return of plasma cortisol levels to normal.

Despite acneiform lesions being a well known accompaniment of high dose, prolonged corticosteroid therapy, temporary improvement, as in the present study, is commonly observed following administration of lower doses in treatment of acne. As stated by Strauss and Pochi (14) cortisol and its analogues need not cause sebaceous gland enlargement and activity except under unphysiological conditions, e.g., above 50 mg hydrocortisone per day as noted by Harrison, *et al.* (15).

The need for explaining improvement associated with systemically absorbed corticosteroids is apparent.

Inasmuch as characteristic hormone effects can be obtained only in the living organism (16), the following interpretations may be offered, notwithstanding obvious reservations regarding biochemical and physiological significance in a complex system of many uncontrolled variables operating in a pathological state. Similarly, although many various effects of corticosteroids have been learned, little is known of the mechanisms involved.

(1) The local action of corticosteroids in acne cysts and adjacent tissue may be influenced by the known alterations produced by these hormones in connective tissue, generally relating to an anti-inflammatory effect.

(2) "Sebotropic" or other permissive pituitary factors as summarized by Loring and Lancaster (17) could conceivably operate in a feed-back system with corticosteroids or their metabolites on sebaceous glands so that suppression of pituitary factors directly or permissively affecting sebaceous activity and acne in addition to pituitary-adrenal suppression could occur.

(3) General effects of pituitary-adrenal suppression in acne are undoubtedly related to absorption and level of exogenous corticosteroids achieved. When this level is enough to produce suppression, replacing and perhaps exceeding normal tissue levels, it may act directly as mentioned under local action or through the influence of an active metabolite (18). Recently, information providing additional considerations in adrenal suppression and effects on acne has become available.

In human castrates, sebaceous activity has been related directly to the output of adrenal androgens (19), in particular, dehydroepiandrosterone (DHA) (20). It has been shown that DHA disappears from plasma shortly after birth to reappear in the second decade at or about puberty (21) which together with testosterone in the male might contribute to the onset of acne at or about puberty.

Since the adrenal cortex secretes DHA in amounts which are probably as great as those of cortisol (18, 22), suppression of this hormone, a potential precursor of testosterone, could be of much more significance than the correspondingly lesser alteration of the other corticosteroid levels whereby exogenous absorption merely replaces or only slightly exceeds endogenous levels. DHA comprises less than 10% of the total urinary 17 ketosteroids, however, explaining the observed poor correlation of urinary 17 ketosteroids with adrenal androgen output (23, 24).

In addition to the suppression of DHA by exogenous corticosteroid, Kirschner, Lipsett and Collins (24) have shown a lesser decrease in plasma testosterone (21% decrease with 20 mg prednisone daily).

The formation of small amounts of labeled testosterone from DHA *in vitro* by incubation of thin slices of adolescent male human skin from both shoulder and thigh areas in the DHA medium reported by Cameron, *et al.* (25) also showed that greater amounts were produced in the shoulder (acne area) than in the thigh (non-acne area). Other metabolites of DHA, androstenedione and androstenediol are known to be about half as potent as methyl testosterone in stimulating sebaceous activity (26) and conversion is also much greater in acne areas of the skin (27). Reports of similar increased androgen conversion from DHA in acne areas have subsequently appeared for are in preparation (27).

On the other hand, higher exogenous corticosteroid doses provide greater excesses over normal endogenous levels and may account for some of the adverse effects observed in high dose corticosteroid therapy. Excess levels of corticosteroids other than DHA could in turn increase sebaceous activity by similar androgen conversion (15) thus, overriding any beneficial anti-inflammatory or DHA suppression effect. According to the hypothesis above, ideal treatment with intralesional or otherwise systemically absorbed corticosteroids in acne would consist of that dose which is just enough to produce adrenal suppression of DHA and possibly testosterone long enough to be effective without resulting in excessive, unphysiologic exogenous levels. Administration should be at intervals great enough to avoid adrenal atrophy and unresponsiveness to stress. Another limiting factor in frequency of intralesional administration of triamcinolone acetonide following this scheme would probably include excessive local accumulation and effects.

From the results of the present study, it would appear that for suppressive action alone, total doses above 15 mg of intralesional triamcinolone acetonide would be adequate provided the duration of suppression is considered separately for the dose employed. Further study is necessary to permit better correlation of dose and duration of suppression with duration and degree of improvement to arrive at a truly minimal effective dose administration interval. Considering the local effects as well, the solubility and potency of the steroid used would then become more important factors.

The concept of a minimal effective dose producing improvement as a result of and approximating the duration of some optimal safe period and degree of adrenal suppression in acne vulgaris is quite different from one which is just short of producing suppression. Certainly, cautious interpretation of adrenal suppression and responsiveness as determined by morning plasma cortisol levels is advised according to (1) the reliability of the methods of administration of drug and plasma cortisol determination, mentioned previously and (2) the reliability of these levels used alone as an adequate indication of adrenal's functional state. In an extensive study by Martin, *et al.* (28) it was shown that there was a decreased ability to raise plasma cortisol appropriate to various stimuli among patients on intermittent corticosteroid treatment. Morning plasma cortisol levels were normal in the treatment group, but fell more rapidly than in the control group at noon.

Deficiencies in response to hypoglycemia were greater than with metapyrone stimulation suggesting that a state of decreased stress responsiveness can persist after normal feedback responsiveness is restored.

Although recovery from adrenal suppression is the rule, it may persist for a long time (29), the true duration of which should be remembered in terms of ability to respond to stress.

Whether DHA or other sources of adrenal androgen can be suppressed by exogenously absorbed corticosteroids and produce a therapeutic effect in acne without causing either atrophy or a potentially dangerous deficiency in stress responsiveness is not known, but deserves further investigation.

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